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Docket No.: 20827 US (C38435/123864)

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )

Werner BONRATH, *et al.* )

Examiner: E. Sackey

Serial No.: 10/053,297 )

Art Unit: 1626

Filed: January 17, 2002 )

For: **PROCESS FOR MAKING VITAMIN E  
USING HYDROGEN-TRIS(OXALATO)  
PHOSPHATE** )New York, New York  
June 10, 2003RESPONSE TO OFFICE ACTIONMail Stop Non-Fee Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450**RECEIVED**

JUN 16 2003

TECH CENTER 1600/2900

Sir:

This is in response to the Office Action mailed March 11, 2003, which set a three-month shortened statutory period for response. Accordingly, this response is filed timely upon mailing, with an executed certificate of mailing, on or before June 11, 2003. 37 CFR § 1.8. No fee is believed to be due. If it is determined that a fee is due, please charge such fee to Deposit Account No. 02-4467. A duplicate copy of this sheet is enclosed.

## REMARKS

### Rejection under 35 USC § 103

Claims 1-22 were rejected solely under 35 USC § 103(a) as being unpatentable over Fürbringer, U.S. Patent No. 5,886,196 ("Fürbringer") in view of GB 811,895 ("GB '895") and Chemical Abstracts 124:248655 ("CA 124:248655"). (Paper No. 6 at 4.)

For the reasons set forth below the rejection, respectfully is traversed.

Fürbringer discloses a catalyst system for condensation reactions employing **hydrogen bis(oxalato)borate** as a protonic acid catalyst. (Col. 1, lines 5-15 and lines 64-67.) Fürbringer discloses the production of d,l- $\alpha$ -tocopherol by reaction of trimethylhydroquinone with isophytol in the presence of the **hydrogen bis(oxalato)borate** catalyst. (Example 6 and see Col. 1, lines 30-32.) Fürbringer notes that the disclosed catalyst avoids disadvantages of previously disclosed catalysts:

All of these previously known processes have serious disadvantages. For example, corrosion problems occur in all processes, and when boron trifluoride is used toxicity problems arise with the boron trifluoride adducts. Also, when iron or zinc is used there is a contamination of the waste water with iron or zinc ions which today is no longer acceptable....The object of the present invention is accordingly to provide a catalyst system for the aforementioned condensation reactions which does not have the disadvantages of the previously known procedures. (Col. 1, lines 41-57.)

GB '895 discloses "a process for the production of esters of  $\alpha$ -tocopherol...." (Page 1, col. 1, lines 9-13.) The process is "characterised in that  $\alpha$ -tocopherol chloracetic acid ester is reacted, preferably at an elevated temperature, with a dialkylamine, e.g. containing 1 or 2 carbon atoms in each alkyl group, in the presence

or absence of an inert solvent therefore e.g. aliphatic or aromatic hydrocarbons....” (Page 1, col. 2, lines 77-85.) The reaction of 2,5,6-trimethylhydroquinonemonochloracetate-(1) with phytol or isophytol and zinc chloride to produce  $\alpha$ -tocopherol chloracetate is specifically disclosed (Example 1b).

CA 124:248655 discloses “a structural and photophysical study” of “chiral, three-dimensional supramolecular compounds: homo- and bimetallic oxalate- and 1,2-dithiooxalate-bridged networks.” (Title.) Specifically disclosed are  $[\text{Cr}(\text{bpy})_3][\text{ClO}_4][\text{NaCr}(\text{ox})_3]$ ,  $[\text{Cr}(\text{bpy})_3][\text{ClO}_4][\text{Mn}_2(\text{ox})_3]$ ,  $[\text{Cr}(\text{bpy})_3][\text{BF}_4][\text{Mn}_2(\text{ox})_3]$ ,  $[\text{Co}(\text{bpy})_3][\text{PF}_6][\text{NaCr}(\text{ox})_3]$ , and  $[\text{Ni}(\text{phen})_3][\text{NaCo}(\text{dto})_3] \cdot \text{C}_3\text{H}_6\text{O}$ .<sup>1</sup>

In making the rejection, the Examiner asserted that Fürbringer discloses “the use of **hydrogen bis(oxalato)borate** catalyst in preparing  $\alpha$ -tocopherol which comprises a reaction mixture between trimethylhydroquinone and isophytol and an organic solvent.” (Paper No. 6 at 4.) The Examiner acknowledged, however, that Fürbringer differs from the presently claimed invention “in that **bis(oxalato)borate** catalyst is used for preparing  $\alpha$ -tocopherol, wherein a catalyst comprising **tris(oxalato)phosphate** is required for the instant process.” (*Id.*)

To fill the acknowledged gap, the Examiner asserted that the “reference catalyst, bis(oxalato)borate is a known nontoxic, non-corrosive and environmentally safe catalyst for producing  $\alpha$ -tocopherol in high yields” and that “[t]he required catalyst of tris(oxalato)phosphate is also nontoxic, non-corrosive and environmentally safe. (*Id.* at 4-5 (internal citations omitted).) The Examiner summarily concluded that “the use of

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<sup>1</sup> bpy = 2,2'-bipyridine; ox = oxalate; phen = phenol; and dto = 1,2-dithiooxalate.

bis(oxalato)borate catalyst is prima facie obvious in view of its properties as disclosed.”

(*Id.* at 5.)

Recognizing the untenable reliance on Fürbringer alone, the Examiner relies on GB '895 and CA 124:248655 in an attempt to fill the gaps:

Additionally, see GB 811,895 which [discloses] the reaction of trimethylhydroquinone and isophytol/phytol with **phosphate (III)** as a catalyst and CA 124:248655 which discloses the equivalence of other known catalyst such as **tris(oxalate)chromate**.” (*Id.*)

The Examiner then asserted that such compounds “are known chelating agents which are non-toxic and non-corrosive catalysts which can be interchangeable with each other because of their similar properties and which can be used to prepare tocopherols.” (*Id.*) The Examiner summarily concluded that “one of ordinary skill in the art would thus have been motivated to prepare  $\alpha$ -tocopherol by exchanging one known catalyst for the other and manipulating process parameters such as ratios, temperature's solvents with the expectation of improving product yield and purity absent a showing of unexpected results. ... The instantly claimed process would therefore have been suggested to one of ordinary skill absent a showing of unexpected properties and/or results.” (*Id.* at 7.)

As is well settled, a rejection under § 103 must demonstrate **where** in the cited documents there was a suggestion which would have “strongly motivated” one to carry out the invention as claimed. *Ex parte Graselli*, 231 USPQ 393, 394 (Bd. App. 1986). The type of motivation which would have “**impelled**” one to do so (*Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993)), and the type of suggestion that the changes “**should**” be made. *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App.

1964). The factual inquiry whether to combine documents must be thorough and searching. And, as is also well settled, the teaching, motivation, or suggestion to combine “must be based on objective evidence of record.” *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002).

It is respectfully submitted that the Examiner has failed to set forth a *prima facie* case for at least five reasons. First, the rejection appears to misconstrue the claimed invention as requiring “bis(oxalato)borate.” Second, the rejection appears to misconstrue GB ‘895’s disclosure of the undesirable use for phosphate (III) in making aliphatic esters of  $\alpha$ -tocopherol in the background section. Third, the rejection fails to identify a single document that discloses the use of hydrogen tris(oxalato)phosphate as a catalyst for making (all-*rac*)- $\alpha$ -tocopherol as claimed. Fourth, the rejection fails to identify any disclosure or suggestion in any of the cited documents of the alleged equivalence of bis(oxalato)borate (Fürbringer), a phosphate (III) catalyst (GB ‘895), tris(oxalato)chromate (CA 124:248655), and tris(oxalato)phosphate as claimed. Fifth, even if the documents identified by the Examiner are combined, they still fail to disclose or suggest the claimed invention.

#### 1. Bis(oxalato)borate Is Not Claimed

As noted above, the Examiner asserts that “the use of bis(oxalato)borate<sup>2</sup> is *prima facie* obvious.” However, that is not what is claimed. Claim 1 recites the use of hydrogen tris(oxalato)phosphate in a process for making (all-*rac*)- $\alpha$ -tocopherol. The

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<sup>2</sup> If the Examiner intended to assert that the use of hydrogen tris(oxalato)phosphate, as claimed, is *prima facie* obvious, then he is requested to reissue the Office Action to accurately state the grounds for rejection.

obviousness of using bis(oxalato)borate has no bearing on patentability of the claimed invention. For this reason alone the rejection is deficient and should be withdrawn.

## 2. GB '895 Teaches Away From The Claimed Invention

A *prima facie* case of obviousness requires that the rejection describe with specificity **why** one skilled in the art would have combined the cited documents to arrive at the claimed invention. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (CAFC 1999). (“Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of *the requirement for a showing of the teaching or motivation to combine prior art references.*”). Moreover, if a proposal for modifying one or more documents renders such documents inoperable or destroys their intended purpose, then the requisite motivation to make the modification would not have existed, and any rejection based on such a proposed modification would have to fail. (See, e.g., *In re Fritch*, 23 USPQ2d 1780, 1783, n. 12 (Fed. Cir. 1992) and *In re Ratti*, 123 USPQ 349, 352 (CCPA 1959) (holding the suggested combination of references improper under § 103 because it “would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] **as well as a change in the basic principles under which [that reference’s] construction was designed to operate.**”))

GB '895 discloses “a process for the production of esters of  $\alpha$ -tocopherol....” (Page 1, col. 1, lines 9-13.) GB '895 specifically notes that “[**f**]ree  **$\alpha$ -tocopherol is hardly used as a pharmaceutical preparation** in view of its high sensitivity to oxidization.” (*Id.* at lines 14-16.)

Contrary to the Examiner's assertion, GB '895 does not disclose "the reaction of trimethylhydroquinone and isophytol/phytol with phosphate (III) as a catalyst." (Paper No. 6 at 5.) Rather, GB '895 teaches away from the reaction of trimethylhydroquinone and isophytol. In Example 1a, for example, 2,5,6-trimethyl-4-hydroxy-1-phenyl-diazoniumchloride is reacted with monochloroacetic acid to produce 2,5,6-trimethylhydroquinonemonochloroacetate-(1) for further reaction with phytol or isophytol to produce  $\alpha$ -tocopherol chloroacetic acid. In purifying the 2,5,6-trimethylhydroquinonemonochloroacetate-(1), the "residue is stirred with low boiling point range petroleum ether and the resulting crystals (trimethylhydroquinone) are filtered off with suction. The mother liquor is evaporated and distilled [and] 2,5,6-trimethylhydroquinonemonochloroacetate-(1) is obtained...." (Page 2, col. 1, lines 19-42.) Accordingly, ***trimethylhydroquinone is removed from the reaction mixture and discarded*** and the 2,5,6-trimethylhydroquinonemonochloroacetate-(1) reserved for further reaction.

2,5,6-Trimethylhydroquinonemonochloroacetate-(1) "is dissolved in benzene and stirred with phytol or isophytol and ***zinc chloride*** on a water bath for five hours while bubbling through carbon dioxide." (Example 1b (page 2, col. 1, lines 43-47) (amounts omitted)). Upon purification  $\alpha$ -tocopherol chloroacetate crystals are obtained. (*Id.* at lines 48-62.)

The only disclosure of phosphate in GB '895 is found in a the background disclosure detailing the problems solved by the claimed invention.

Aliphatic esters of  $\alpha$ -tocopherol, however, have the disadvantage that they are insoluble in water, a fact which leads to disadvantageous resorption conditions. This undesirable state of affairs has hitherto been remedied by

esterification with polybasic acids, e.g. phosphoric or succinic acids, and converting into water soluble acid esters salts. ***This procedure***, however, ***has had little success*** because the said polybasic acid esters are stable only in neutral or weakly alkaline solution. In the presence of acids, for example in the stomach or in acid cell medium, water insoluble acid esters are regenerated from said acid ester salts. (Page 1, col. 1, lines 19-32.)

Thus contrary to the assertion in the Office Action that GB '895 "teaches the reaction of trimethylhydroquinone and isophytol/phytol with phosphate (III)," GB '895 actually discloses that "polybasic" phosphate may be used in a esterification reaction with aliphatic esters of  $\alpha$ -tocopherol. Such a reaction, however, "has had little success." (*Id.*) Moreover, the rejection provides no technical reasoning or evidence from the cited documents to explain why one skilled in this art would ignore the express disclosure in GB '895 that using polybasic phosphate would have "little success."

In summary, GB '895 teaches away from the claimed invention is at least four distinct ways: 1) the production of  $\alpha$ -tocopherol esters is disclosed to solve the problem associated with free  $\alpha$ -tocopherol, 2) the reaction of trimethylhydroquinone and phytol or isophytol is explicitly precluded, 3) a zinc chloride catalyst is disclosed, which bears no resemblance to the hydrogen tris(oxalato)phosphate catalyst of the present invention, and 4) the use of phosphate as a catalyst is specifically discouraged. In short, the Examiner has pointed to no evidence or reasoning why one would ignore the explicit disclosure of GB '895 to arrive at the claimed process. That, however, was the Examiner's burden. Having failed to meet this burden, the rejection is legally deficient and must be withdrawn.

Moreover, the proposal to modify Fürbringer to employ the catalyst of GB '895 would destroy the intended purpose of Fürbringer. The catalyst of Fürbringer is



designed to avoid the disadvantages of previously used catalysts. For example, "when iron or zinc is used there is a contamination of the waste water with iron or zinc ions which today is no longer acceptable." (Col. 1, lines 44-47.) GB '895, however, discloses the use of a "zinc chloride" catalyst. (Page 2, col. 1, lines 14 and 46.) As noted above, if a proposed modification destroys the intended purpose of the cited document then the requisite motivation to make such modification is absent, and any rejection based on the modification must fail. Because the modification suggested by the Examiner would be in direct contradiction to the clearly stated purpose of Fürbringer, the motivation to make this modification is missing. Accordingly, the rejection must be withdrawn for this reason also.

### **3. The Rejection Fails To Identify A Single Documents That Discloses Tris(oxalato)phosphate**

CA 124:248655 discloses "a structural and photophysical study" of "chiral, three-dimensional supramolecular compounds: homo- and bimetallic oxalate- and 1,2-dithiooxalate-bridged networks." (Title.) Nowhere does CA 124:248655 disclose or suggest a hydrogen tris(oxalato)phosphate catalyst. CA 124:248655 discloses compounds with "an elaborate structure of cationic and anionic species within a polymeric anionic network." Each compound requires three components: 1) a chromium or cobalt bipyridine cation, 2) an oxalate bridged metal complex containing two metal atoms; and 3) a complex anion.<sup>3</sup>

The Examiner asserted that CA 124:248655 "discloses the equivalence of other known catalyst such as tris(oxalate)chromate." (Paper No. 6 at 5.) CA

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<sup>3</sup> A compound ( $[\text{Ni}(\text{phen})_3][\text{NaCo}(\text{dto})_3] \cdot \text{C}_3\text{H}_6\text{O}$ ) in which the oxalate bridging ligand is substituted with a dithiooxalate is also disclosed.

124:248655, however, is devoid of any disclosure that the identified compounds, let alone tris(oxalato)phosphate as claimed, may be used as a catalyst. CA 124:248655 discloses only that the identified oxalate components are "oxalate-bridged metal complexes." The Examiner's suggested modification requires removing this component from the disclosed compound; modifying the component by substituting a single phosphorus atom for the two transition metal atoms of the component; and substituting the thus modified component for the catalyst of Fürbringer. The Examiner has not, however, offered any evidence from any of the cited documents or technical reasoning why one would have been motivated to carry out any of these steps, much less all of them. It was, however, the Examiner's burden to supply evidence supporting the proposed modification. Because the Examiner has failed to provide such evidence, the rejection is infirm as a matter of law, and should be withdrawn for this reason too.

Modifying the selected component of CA 124:248655 in the manner suggested by the Examiner would make the component incapable of being either a bridged or a metal complex. The component would therefore be incapable of producing the "elaborate structure of cationic and anionic species within a polymeric anionic network." Accordingly, the modification destroys the intended purpose of CA 124:248655, namely the production of "homo- and bimetallic oxalate ... bridged networks" for "structural and photophysical study." As noted above, when a rejection suggests a modification that destroys the intended purpose of a cited document, the requisite motivation to carry out that modification is missing. Because the rejection relies on a modification which would destroy the intended purpose of CA 124:248655, and has failed to provide any technical reasoning or citations to the other cited

documents why one would make the proposed modifications to CA 124:248655, the rejection must be withdrawn.

#### **4. The Rejection Provides No Evidence That The Reference Compounds Are Equivalent**

The rejection also fails to identify any disclosure or suggestion on any of the cited documents that the chromium oxalate bridged networks of CA 124:248655, the zinc chloride catalyst disclosed in GB '895 (or even the polybasic phosphoric acid compounds distinguished by GB '895), the bis(oxalato)borate compounds of Fürbringer and the tris(oxalato)phosphate compounds as claimed are in any way equivalent. But that too was the Examiner's burden. Without such a showing or suggestion of equivalence, the rejection is nothing more than conjecture and a wish. For this reason also, the rejection should be withdrawn.

#### **5. Even If Combined, The Documents Do Not Disclose/Suggest The Claimed Invention**

As is well settled, obviousness cannot be based upon speculation, nor can obviousness be based upon possibilities or probabilities. Obviousness *must* be based upon facts, "cold hard facts." *In re Freed*, 165 USPQ 570, 571-72 (CCPA 1970). When a conclusion of obviousness is not based upon facts, it cannot stand. *Ex parte Saceman*, 27 USPQ2d 1472, 1474 (BPAI 1993). Further, "to establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." MPEP § 2143.03 citing *In re Royka*, 180 USPQ 580 (CCPA 1974).

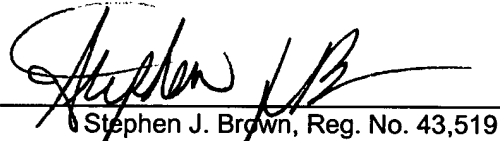
Even if Fürbringer, GB '895, and CA 124:248655 are properly combinable, which is not admitted, the proposed combination does not produce the process as recited in claim 1. Fürbringer discloses a catalyst system for condensation reactions

which employs hydrogen bis(oxalato)borate. The claimed invention recites a hydrogen tris(oxalato)phosphate catalyst. There are two distinct structural differences between these two catalysts. First, hydrogen bis(oxalato)borate has only two ("bis") oxolate moieties and hydrogen tris(oxalato)phosphate has three ("tris"). Second, the central atoms of the two catalysts are different, e.g., boron vs. phosphorus. To bridge this gap, the Examiner relied upon GB '895 and/or CA 124:248655. However, neither GB '895 nor CA 124:248655 discloses or suggests anything which closes this gap.

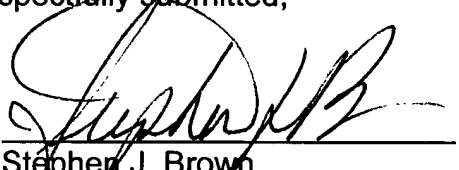
GB '895 discloses zinc chloride as a catalyst, and CA 124:248655 is absolutely silent as to catalysts, but discloses "an elaborate structure of cationic and anionic species within a polymeric anionic network." Accordingly, even if the catalyst of GB '895 or a compound of CA 124:248655 is substituted for the catalyst of Fürbringer one does not arrive at the process claimed. At best, one is left with a reaction catalyzed by zinc chloride or an "elaborate structure of cationic and anionic species within a polymeric anionic network." Simply stated, that is not what is claimed. The Examiner has pointed to nothing in any of the cited documents, alone or in combination, which discloses or suggests the use of hydrogen tris(oxalato)phosphate as a catalyst as claimed. For this reason the rejection is factually deficient and should be withdrawn.

Accordingly, for the reasons set forth above, withdrawal of the rejection and allowance of the claims are respectfully requested. If the Examiner has any questions regarding this paper, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on June 10, 2003.

  
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Respectfully submitted,

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